Fermented dairy products, calcium, and colorectal cancer in The Netherlands Cohort Study

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Fermented Dairy Products, Calcium, and Colorectal Cancer in the Netherlands Cohort Study[1]

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ABSTRACT

Experimental studies suggest that an increased consumption of fermented dairy products and calcium might decrease the risk of colorectal cancer. The associations between fermented dairy products, dietary calcium, and colorectal cancer risk were investigated in a population with a wide variation in intake of dairy products.

The Netherlands Cohort Study of diet and cancer started in 1986 when 120,852 Dutch men and women, ages 55–69, filled out a questionnaire concerning dietary patterns and lifestyle. The present analysis is based on 3.3 years of follow-up and includes 215 incident cases of colon cancer and 111 incident cases of rectal cancer, excluding cases diagnosed in the first year of follow-up. After adjustment for potential confounding variables, colorectal cancer risk was weakly inversely associated with the consumption of fermented milk [relative rate (RR) in the highest category of intake compared to nonusers, 0.89; 95% confidence interval (CI), 0.60, 1.33], unfermented milk (RR, 0.86; 95% CI, 0.57, 1.29), and cheese (RR, 0.88; 95% CI, 0.59, 1.33). However, category-specific relative rates and tests for trends were not statistically significant. For fermented milk, the inverse association was limited to colon cancer (RR, 0.70; 95% CI, 0.43, 1.15; trend, $P = 0.33$). In crude and multivariate models, total dietary calcium intake (highest *versus* lowest quintile, RR, 0.92; 95% CI, 0.64, 1.34) and calcium from fermented dairy products (RR, 1.14; 95% CI, 0.77, 1.68) were not significantly associated with colorectal cancer risk. Calcium from unfermented dairy products was inversely associated with rectal cancer risk (RR, 0.55; 95% CI, 0.30, 1.04; trend, $P = 0.03$).

After 3.3 years of follow-up, these data are not consistent with a substantially decreased risk of colorectal cancer with increased intake of fermented dairy products and dietary calcium.

INTRODUCTION

Colorectal cancer is one of the major types of cancer in Western society. In the Netherlands, yearly, about 48 new cases of colorectal cancer (30 colon, 18 rectum) are diagnosed per 100,000 men and 49 cases per 100,000 women (35 colon, 14 rectum). Colorectal cancer is the third most common cancer in Dutch men and the second most common cancer in Dutch women (1). Because its incidence is still rising, treatment is difficult, and mortality remains high, emphasis should be placed on preventive measures. In addition to dietary recommendations against cancer in general, such as a higher consumption of vegetables and fruits (2), other relatively simple and feasible dietary changes might add to the prevention of colorectal cancer.

The possible protective role of fermented dairy products such as yogurt, buttermilk, and cheese, originally proposed by Metchnikoff (3) in the beginning of this century, has regained attention in the past decade. Establishment of certain lactobacilli in the gastrointestinal tract could contribute to the stabilization of the colonic flora and exert beneficial effects on the host. In recent experiments, the activity of carcinogen-producing fecal enzymes was decreased in subjects given supplements of *Lactobacillus* cultures (4, 5), and *in vitro* studies of human lymphocytes suggest that lactobacilli stimulate the immune system locally, as well as systemically (6, 7).

In addition to these mechanisms mediated by microorganisms, fermented dairy products contribute substantially to our daily calcium intake. In the Netherlands, about 70% of calcium intake is of dairy origin, half of which is from fermented dairy products. It is hypothesized that calcium (8) or, more recently, that calcium phosphate (9) binds free fatty acids and bile acids, thereby reducing the effective toxic dose to the colonic epithelial cells and their subsequent proliferative response. Calcium might also directly influence cell proliferation by inducing cell differentiation (10).

Although several epidemiological studies have investigated the relationship between dairy product consumption, calcium intake, and colorectal cancer (11–22) or colorectal polyps (23), only a few addressed the association with fermented dairy products (14, 16, 17, 20, 23). In two population-based case-control studies of colon cancer, an inverse association was observed for yogurt (OR[4] = 0.83 for 10 servings/month, 95% CI = 0.70, 0.98) (20) and cultured milk consumption (OR = 0.65, 95% CI = 0.41, 1.01) (16), adjusted for potential confounding variables. In two companion American prospective studies, the 1980–1988 follow-up of the NHS (121,700 women) and the 1986–1990 follow-up of the HPFS (51,529 men), a nonsignificant inverse association with yogurt consumption and colorectal polyps was found (for more than 4 times/week, 1 cup *versus* almost never: NHS, RR = 0.60, 95% CI = 0.30, 1.18; HPFS, RR = 0.66, 95% CI = 0.28, 1.46), which diminished in the HPFS after adjustment for covariates (RR = 0.89) (23).

Although cheese consumption contributes significantly to saturated fat intake, in several case-control studies (14, 16, 18) and one prospective study (17) the consumption of this product was not strongly associated with colorectal cancer risk (RR = 0.9, 0.7, 1.1, and 1.1, respectively).

The studies mentioned above have mainly been conducted in countries in which the consumption of yogurt or cultured milk is not integrated in traditional food habits. In countries in which the consumption of fermented milk is high and heterogeneous, the comparison of risks between high- and low-consumption categories would be most powerful. The Dutch have a longstanding tradition of fermented dairy product consumption (*e.g.*, per capita annual consumption of yogurt in the Netherlands is 18.9 *versus* 2.1 kg in the United States; 24). In two case-control studies conducted in the Netherlands, inverse associations were observed between breast cancer and fermented dairy product consumption (25) and cancer of the exocrine pancreas and fermented dairy product consumption (26). We studied prospectively the association between these products and calcium and colorectal cancer in the ongoing Netherlands Cohort Study of diet and cancer (27).

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[4] The abbreviations used are: OR, odds ratio; CI, confidence interval; NHS, Nurses Health Study; HPFS, Health Professionals Follow-Up Study; RR, relative rate.

SUBJECTS AND METHODS

The cohort characteristics and the method for cancer follow-up have been described (27). Briefly, the study was initiated in 1986 when 58,279 men and 62,573 women aged 55 to 69 years completed a self-administered baseline questionnaire inquiring after food habits and potential confounding factors. Following the case-cohort approach for analysis of the data, a subcohort of 3500 persons (1688 men, 1812 women) was randomly sampled from the baseline cohort and followed up for vital status to estimate the person time contributed by the entire cohort. No subcohort members were lost to follow-up. Incident cancer cases occurring in the cohort were identified by record linkage to cancer registries and a nationwide pathology register (28). The analysis in this report was restricted to 3.3 years of follow-up from September 1986 (baseline) to December 1989. The completeness of cancer follow-up was estimated to be 95% (29).

Food Frequency Questionnaire. The semiquantitative food frequency questionnaire included 150 food items and concentrated on habitual food and beverage intake during the preceding year (30). The daily amounts of 9 dairy items were estimated from the number of glasses (milk, chocolate milk, buttermilk), number of cups (yogurt, curds, custards with and without dietary fiber), or number of sandwiches filled (cheese and low-fat cheese). In addition, consumption of cheese as a meat substitute with the hot meal was asked for.

The questionnaire was validated against a 9-day dietary record (30). The sex- and energy-adjusted Pearson coefficient of correlation for dietary calcium was 0.62. The Spearman coefficient of correlation for milk and milk products was 0.60 and for cheese 0.61. To minimize observer bias in coding and interpretation of the data, questionnaires were key-entered twice and processed without knowledge of case/subcohort status.

Data Analysis. Subjects who reported a history of cancer other than skin cancer in the baseline questionnaire were excluded. A total of 3346 subcohort members (1630 men, 1716 women) and 478 incident cases (312 colon, 166 rectum; 258 men, 220 women) remained available for analysis. Furthermore, 7% of these subjects were excluded because of incomplete or inconsistent dietary data (29). Therefore, 3111 subcohort members and 443 colorectal cancer cases (293 colon, 150 rectum), 12 of which were members of the subcohort, were included in the analysis. Because subclinical symptoms of colorectal cancer may influence dietary habits before diagnosis, data were analyzed without taking the first year of follow-up into consideration (3083 subcohort members, 215 colon cancer and 111 rectal cancer cases).

Categories of dairy product intake were based on the subcohort distribution with nonusers taken as the reference. Additional analyses were conducted excluding nonusers and taking the lowest category of intake as the reference. For nutrient intakes, quintiles based on the subcohort distribution were used in the analysis. Since subjects tend to skip items they do not consume (31), persons with missing data for a relevant dairy product were treated as nonusers. We verified this assumption by conducting analyses including a variable indicating those with missing data for one of the specific foods.

In this cohort, the major fermented dairy products were buttermilk (39% of total consumption in grams), yogurt (39%), fat cheese (16%), and curds (6%). Because of their low contribution, curds are not taken into account in analyses of products. The fermented milks (yogurt and buttermilk), which differ from cheese with respect to their consumption pattern, were treated as one food group. With respect to cheese, analyses were restricted to full-fat cheese (95% hard cheese) which accounts for about 90% of cheese consumption in this cohort.

In this population, the consumption of yogurt and buttermilk was positively, although not strongly, correlated (r = 0.13).

Mean daily nutrient intake was calculated from mean food intakes using the computerized Dutch food composition table (32). Energy-adjusted nutrient intakes were based on residuals from the regression of nutrient intake on total energy intake (33). Since exact amounts of calcium in the various supplements used were not available, calcium supplement use [alone (91%) or in combination with vitamin D] is examined as a dichotomous variable (use "yes" or "no"). Since <1% of the subcohort uses specific vitamin D supplements, these supplements were not taken into account in these analyses.

The case-cohort approach was used for data analysis (34). Specific programs were developed to account for the additional variance introduced by estimating the person time-at-risk for the subcohort instead of for the entire cohort (29).

Apart from the known risk factors for colorectal cancer (age, family history of large bowel cancer, history of gallbladder surgery (35), the following variables were evaluated as potential confounders using multivariate models: smoking, level of education, any vitamin supplement use, intake of energy, and energy-adjusted intake of fat and dietary fiber. Cases with missing data on covariates were excluded from the multivariate analyses.

Vitamin D intake through sun exposure and from foods could not be adequately assessed and was not taken into account in these analyses.

In addition, analyses were conducted for colon and rectal cancer separately.

RESULTS

Daily intake of yogurt and buttermilk together (median) ranged from 0 g/day in the lowest to 267 g/day in the highest category of intake. For hard cheese consumption, the intake ranged from 0 in the lowest to 37 g/day in the highest category. Intake of calcium ranged from 546 mg in the lowest quintile to 1344 mg in the highest quintile; after energy adjustment these medians were 581 and 1286 mg/day, respectively.

Table 1 shows various characteristics of subcohort members according to high and low intake of fermented milk and calcium. Those who never consumed yogurt or buttermilk did not differ greatly regarding age, energy intake, and calcium/phosphate ratio from those in the highest category of intake. Energy-adjusted intake of fat was higher, while energy-adjusted dietary fiber intake was lower in the lowest category of fermented milk intake. Women consumed yogurt and buttermilk more frequently than men (Table 1; median daily intake among users: women, 96 g; men, 79 g), whereas cheese consumption was similar for both genders (median daily intake among users, 19 g). Body mass index and a positive family history for colorectal cancer did not differ appreciably between the two categories of intake. Among the highest category of intake, a history of gallbladder surgery was reported more frequently, and educational level was higher. The nonuser group included more current smokers. Calcium supplements were used more frequently by those with the highest intake.

Hard cheese consumption was positively associated with energy intake and educational level (data not shown).

Calcium intake was positively associated with energy intake, but no important associations of calcium were observed with age, gender, energy-adjusted intake of fat and dietary fiber, body mass index, family history of colorectal cancer, history of gallbladder surgery, educational level, or smoking status (Table 1). The calcium/phosphate ratio was higher and calcium supplements (alone or in combination with vitamin D) were more frequently used by those with the highest dietary calcium intake. Previous publications provide differences between cases and subcohort members for several nondairy variables (36, 37).

Table 2 shows the RR of colorectal cancer according to dairy product consumption. After adjustment for age and gender, consumption levels for fermented milk, cheese, and unfermented milk were weakly inversely related to colorectal cancer risk. However, for fermented and unfermented milk, none of the category-specific relative rates or trends were statistically significant. For yogurt and buttermilk separately, similar nonsignificantly decreased risks were observed: RR for highest *versus* lowest intake was 0.89 (95% CI = 0.65, 1.21) for yogurt and 0.94 (95% CI = 0.68, 1.30) for buttermilk. The associations with fermented dairy products tended to be most pronounced in women: RR for highest *versus* lowest intake was 0.81 (95% CI = 0.46, 1.44) for fermented milk and 0.61 (95% CI = 0.34, 1.09) for hard cheese.

Adjustment for other potentially confounding variables in multivariate analysis did not change the results appreciably (Table 2). Education level, supplement use, and smoking status were not included in the models

Table 1 *Characteristics of subcohort members (n = 3111) according to high and low intake of fermented milk and calcium*

Variables	Fermented milk[a]		Calcium	
	Non-users	Highest category of intake	Lowest quintile of intake	Highest quintile of intake
Age (yr, mean ± SD)	61.8 ± 4.2	61.5 ± 4.2	61.5 ± 4.1	61.2 ± 4.2
Gender (% men)	60.6	39.2	49.0	49.0
Dietary factors (mean ± SD)				
Fermented milk (g/day)	0	303 ± 116	34 ± 51	165 ± 163
Hard cheese (g/day)	17 ± 18	21 ± 19	8 ± 8	33 ± 24
Unfermented milk (g/day)	114 ± 162	91 ± 134	28 ± 49	233 ± 204
Calcium (mg/day)[b]	814 ± 281	1146 ± 272	633 ± 135	1300 ± 248
Energy (kJ/day)	8102 ± 2282	7967 ± 2100	6738 ± 1790	9356 ± 2311
Total fat (g/day)[b]	86 ± 17	79 ± 16	85 ± 15	82 ± 18
Dietary fiber (g/day)[b]	26 ± 7	29 ± 7	26 ± 6	28 ± 8
Calcium/phosphate ratio	0.6 ± 0.1	0.7 ± 0.1	0.5 ± 0.1	0.8 ± 0.1
Medical and lifestyle factors				
Body mass index (kg/m²)	25.0 ± 3.2	25.3 ± 3.2	25.1 ± 3.3	24.9 ± 2.9
Gallbladder surgery (%)	7.6	11.7	10.1	9.4
Family history of colorectal cancer (%)	5.0	5.7	5.1	5.5
High level of education (%)	11.4	15.4	10.0	13.3
Current smokers (%)	42.1	21.6	35.6	27.9
Calcium supplement users (%)[c]	1.8	5.5	2.2	4.8

[a] Buttermilk and yogurt.
[b] Adjusted for total energy intake by regression analysis.
[c] Includes only calcium (91%) or calcium in combination with vitamin D or magnesium.

since they did not affect the estimates. Additional adjustment for total calcium intake or inclusion of cases diagnosed during the first year of follow-up did not change the results either (data not shown).

The inverse association with fermented milk was restricted to colon cancer (multivariate RR for highest *versus* lowest intake: colon, 0.70; 95% CI = 0.43, 1.15; χ^2 trend = 0.23; rectum, 1.38; 95% CI = 0.74, 2.57; χ^2 trend = 0.25).

Former analyses assume that those who skipped relevant dairy items in the questionnaire were nonusers. When analyses were repeated, including an indicator variable for these subjects, RR estimates for fermented milk, cheese, and unfermented milk did not change appreciably (RR = 0.90, 0.85, and 0.95, respectively). Excluding nonusers from the analyses and choosing the lowest category of consumption as the reference altered the RRs slightly (RR = 0.96, 1.21, and 1.10, respectively).

Table 3 presents the observed relative rates for energy-adjusted dietary calcium intake and calcium from different dietary sources. After adjustment for age and sex and in multivariate models, total dietary calcium and calcium from fermented dairy products were not strongly associated with colorectal cancer risk, while calcium from unfermented dairy products tended to be inversely and calcium from nondairy products positively associated. The nonsignificant inverse association with calcium from unfermented milk and the positive association with nondairy calcium were most pronounced for rectal cancer (RR highest *versus* lowest quintile for unfermented dairy calcium = 0.55, 95% CI = 0.30, 1.04, χ^2 trend = 4.57; RR for nondairy calcium = 2.32; 95% CI = 1.02, 5.28, χ^2 trend = 5.67).

Calcium supplement use was not associated with risk (multivariate RR of users *versus* nonusers = 0.95, 95% CI = 0.50, 1.78).

When analyses were conducted in terms of the calcium/phosphate ratio (RR per difference of 0.1 = 0.94, 95% CI = 0.85, 1.04) or stratified according to gender, results remained similar (data not shown).

DISCUSSION

These data do not support a protective role of fermented dairy products or calcium in colorectal cancer risk. Although risks of colon and rectal cancer were inversely associated with fermented milk consumption and calcium intake from unfermented dairy products respectively, none of the relative rates were significantly different from unity.

A potential drawback of this study is the short follow-up period, *i.e.*, 3.3 years. Especially when gastrointestinal complaints in the time

Table 2 *Relative rates of colorectal cancer according to consumption of dairy products, excluding first year of follow-up*

Average daily intake (g)	Subcohort members	Cases	Relative rates (95% CI) Age and gender adjusted		Multivariate[b]		χ^2 for trend[a] (*P* value)
Fermented milk[c]							
Nonusers	719	85	1.00		1.00		0.10 (0.75)
<30	561	49	0.82	(0.56, 1.20)	0.83	(0.56, 1.21)	
30–90	569	67	1.07	(0.76, 1.52)	1.10	(0.77, 1.56)	
90–180	732	76	0.91	(0.65, 1.28)	0.93	(0.66, 1.31)	
≥180	502	49	0.90	(0.61, 1.32)	0.89	(0.60, 1.33)	
Hard cheese							
Nonusers	394	48	1.00		1.00		0.32 (0.57)
<15	1173	104	0.69	(0.48, 0.99)	0.67	(0.47, 0.97)	
15–30	860	107	0.90	(0.62, 1.30)	0.94	(0.65, 1.37)	
≥30	656	67	0.82	(0.55, 1.21)	0.88	(0.59, 1.33)	
Unfermented milk[d]							
Nonusers	1126	130	1.00		1.00		0.70 (0.40)
<120	819	77	0.79	(0.58, 1.07)	0.81	(0.59, 1.09	
120–240	785	83	0.90	(0.66, 1.21)	0.90	(0.67, 1.22)	
>240	353	36	0.85	(0.57, 1.26)	0.86	(0.57, 1.29)	

[a] Multivariate model.
[b] Adjusted for age, gender, family history of colorectal cancer, intake of energy, energy-adjusted intake of fat and dietary fiber, body mass index, history of gallbladder surgery.
[c] Buttermilk and yogurt.
[d] Whole milk and skim/low-fat milk.

Table 3 *Relative rates of colorectal cancer for quintiles of dietary calcium intake, excluding first year of follow-up*

Nutrient	Level of consumption (quintile) 1	2	3	4	5	χ^2 for trend (*P* value)
Total dietary calcium[a]						
No. of cases	98	89	87	81	88	
No. in subcohort	623	619	622	627	620	
Median intake in subcohort (mg/day)	596	768	893	1032	1288	
Age- and gender-adjusted RR	1.00	0.83	0.96	0.92	0.93	0.03 (0.87)
Multivariate RR[b]	1.00	0.84	0.96	0.93	0.92	0.02 (0.89)
95% CI		0.58, 1.22	0.67, 1.39	0.64, 1.36	0.64, 1.34	
Calcium from nondairy products						
No. of cases	91	82	95	93	82	
No. in subcohort	621	625	622	621	622	
Median intake in subcohort (mg/day)	238	284	318	356	417	
Age- and gender-adjusted RR	1.00	1.14	1.51	1.28	1.25	1.77 (0.18)
Multivariate RR[b]	1.00	1.27	1.82	1.64	1.77	6.56 (0.01)
95% CI		0.83, 1.92	1.21, 2.74	1.05, 2.56	1.08, 2.90	
Calcium from fermented dairy products[c]						
No. of cases	81	87	94	95	86	
No. in subcohort	625	620	621	628	617	
Median intake in subcohort (mg/day)	64	181	287	394	634	
Age- and gender-adjusted RR	1.00	0.96	1.20	1.10	1.07	0.41 (0.52)
Multivariate RR[b]	1.00	1.01	1.29	1.18	1.14	0.98 (0.32)
95% CI		0.69, 1.48	0.89, 1.88	0.80, 1.72	0.77, 1.68	
Calcium from unfermented dairy products						
No. of cases	110	85	78	93	77	
No. in subcohort	622	625	616	624	624	
Median intake in subcohort (mg/day)	45	150	238	345	540	
Age- and gender-adjusted RR	1.00	0.78	0.70	0.81	0.72	2.65 (0.10)
Multivariate RR[b]	1.00	0.78	0.69	0.79	0.71	2.60 (0.11)
95% CI		0.54, 1.11	0.48, 1.01	0.55, 1.14	0.48, 1.05	

[a] Adjusted for total energy intake by regression analysis. Total dietary calcium does not include calcium supplements.
[b] Adjusted for age, gender, family history of colorectal cancer, intake of energy, energy-adjusted intake of fat and dietary fiber, body mass index, history of gallbladder surgery.
[c] Yogurt, buttermilk, cheese, curds.

span before diagnosis would have changed dairy product intake, this could have altered the associations. However, the similarity of results observed in the data with and without cases diagnosed within the first year of follow-up does not support this possibility. Our questionnaire inquired after dietary patterns in the preceding year and might not be representative over a longer period. However, this is a population of elderly people, who are usually considered to have stable food patterns. This stability is confirmed by a repeatability study, in which the food frequency questionnaire was readministered in 5 consecutive years after baseline assessment. It indicated fairly stable nutrient intakes over time.[5] Furthermore, the consumption of these sour fermented milk products is strongly related to preference, which makes it reasonable to assume that the intake of these products does not change dramatically over the years.

The absence of an observed association is not likely to be explained by insufficient contrast in the population. In our cohort, the intake of yogurt and buttermilk varied from 0 in the lowest category to a median of 267 g/day in the highest one according to the questionnaire data and for cheese from 0 in the lowest to 37 g/day in the highest category. Despite a lower per capita intake (24) and presumably a smaller range of intake in the United States, in two American colon cancer case-control studies (16, 20) a significant protective effect was found for cultured milk and yogurt. However, no important associations between fermented dairy products and colorectal polyps were found in the NHS and the HPFS, two American prospective studies (23). In a Dutch breast cancer case-control study (133 cases, 289 population controls), women with a daily intake of 225 g of fermented milk had a 45% lower risk (OR = 0.55, 95% CI = 0.24, 1.27) than nonusers (25). An odds ratio of 0.49 (95% CI = 0.14, 1.76) was found for those women who consumed 20–40 g of cheese/day compared to nonusers (25). In a Dutch case-control study of pancreatic cancer, an inverse association with fermented milk products (highest *versus* lowest quintile of intake OR = 0.37, $P < 0.05$) and cheese (OR = 0.44, $P > 0.1$) was observed (26).

The apparent contradiction of results from epidemiological studies and experimental studies examining lactobacilli is intriguing (4–7) but might be explained by differences in bacterial strains. In most experiments *Lactobacillus acidophilus* is used, which passes the stomach and survives the gastrointestinal tract, whereas *Lactobacillus bulgaricus, Streptococcus thermophilus, Streptococcus lactis*, and *Streptococcus tremor*, which are most frequently used in yogurt and buttermilk, are less resistant to acidic conditions in the stomach (38).

Compared to fermented dairy products, the association between calcium consumption and colorectal cancer risk has been studied more often in epidemiology. However, results are not consistent: some studies found an inverse association (11–13, 19, 20), while others found only a weak nonsignificant inverse association (17, 22, 39) or no association at all (18). Until now, only a few prospective studies, using a validated food frequency questionnaire, investigated the association between calcium intake and colon cancer (22) or colorectal adenomas (23). In the Iowa Women's Health Study (22), after 4 years of follow-up, higher intakes of total calcium (including supplements) and milk products were associated with a 20–30% reduction in colon cancer risk. However, the multivariate adjusted estimates and the χ^2 for trend were not statistically significant, and dietary calcium was not associated with risk (RR = 0.95, 95% CI = 0.57, 1.61). In the NHS and HPFS no associations with total or dietary calcium and colorectal polyps were observed (RR for highest *versus* lowest intake of total calcium: NHS, 1.17, 95% CI = 0.81, 1.69; HPFS, 1.13, 95% CI = 0.76, 1.66) (23).

Our results apply to an elderly population. Since calcium metabolism in pre- and postmenopausal women might be different, our results might not be applicable to a younger generation. However, in the NHS, which studied a younger age group, no association between

[5] R. A. Goldbohm *et al.*, unpublished data.

the occurrence of colorectal adenomas and calcium intake was observed (23).

Median calcium intake ranged from 546 mg/day in the lowest quintile to 1344 mg/day in the highest quintile. According to the calculations of Newmark *et al.* (8), a daily intake of 1500 mg calcium is necessary for individuals with a high-fat (150 g/day), high-phosphate (1500 mg/day) diet to neutralize the fatty acid and bile acid concentrations in the bowel. This implies that a substantial proportion of participants in our study should have been consuming an adequate amount of calcium to experience the biological effects, especially since fat intake was lower than used in the calculations of Newmark *et al.* (8).

The differences in relative risk observed for calcium from different dietary sources might be a chance finding. The range of calcium intake from nondairy products is about one-third of that from dairy products, resulting in less stable estimates. Furthermore, the nondairy group is a mixture of different food items, such as vegetables, coffee, and tea, which makes these findings difficult to interpret.

Exposure to sunlight, the most important source of vitamin D, was not taken into account, since no validated method of sunlight exposure assessment using a self-administered questionnaire was available. Since our national nutrient database did not include vitamin D and supplements only including vitamin D are rarely used in this cohort, vitamin D intake could not be studied. In contrast to the United States, Dutch dairy products are not supplemented with vitamin D.

In summary, the intake of fermented dairy products and dietary calcium is not significantly associated with colorectal cancer risk in this elderly population with a relatively wide variation in dairy product consumption. Although a weak nonsignificant inverse association with colon cancer was observed, the protective effect of fermented dairy products as seen in experimental studies could not be confirmed in this prospective study with a follow-up period of 3.3 years.

Although similar results were found when analyses were conducted with and without cases diagnosed during the first year of follow-up, a longer follow-up time is needed to be certain that no changes in dairy product consumption occurred as a result of subclinical disease. Moreover, it remains worthwhile to study gender differences and differences between various sites within the large bowel.

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